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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	SPR data were collected with Biacore 8K Control Software v2.0.15.12933. ELISA plates were measured with the reader software Gen5 Version 1.11.5, BioTek Instruments, Inc. DLS measurements were performed using Dynamics v7.1.7.16, Wyatt Tecnology Corp. The building of bispecific antibody was performed using ALMOST toolkit version 1 and Pymol 2.4. The Molecular Dynamics simulations were performed using Gromacs 2020.2. LightCycler® 480 Software, Version 1.5 Modulus II Microplate Reader User interface version 2.1.0 by TURNER BioSystems I-TASSER Suite 5.1 ImageJ Version 1.53h
Data analysis	SPR data were analyzed with Biacore Inside Evaluation Software v2.0.15.12933. DLS data were analyzed using Dynamics v7.1.7.16 (Wyatt Tecnology Corp.) Data from ELISA and mouse experiments were analyzed with GraphPad Prism Version 8.4.2. The 3D structures were analyzed using Pymol 2.4. The MD trajectories were analyzed using Gromacs 2020.2 Microsoft Excel 2016 BioEdit Sequence Alignment Editor, version 7.2.0.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The authors declare that data supporting the findings of this study are available within the paper and its supplementary information files. All other data are available from the corresponding author upon reasonable request. Published data were taken from GenBank (https://www.ncbi.nlm.nih.gov/genbank/), UniProt (https://www.uniprot.org/), Protein Data Bank, PDB (https://www.rcsb.org/) and ViPR database (https://www.viprbrc.org/).

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample-size calculation was performed. The sample sizes were chosen based on experience and previously published papers (e.g., Zost et al., Nature. 2020 Aug;584(7821):443-449. doi: 10.1038/s41586-020-2548-6.; Hassan et al., Cell. 2020 Aug 6;182(3):744-753.e4. doi: 10.1016/j.cell.2020.06.011.). Details about groups and sample sizes for mouse virus challenge studies are provided in the manuscript and figure legends.
Data exclusions	No data were excluded.
Replication	Experiments successfully repeated at least twice.
Randomization	The mice were randomly assigned to cages and the cages were then randomized into groups.
Blinding	Blinding was not relevant to this study, except lung pathology evaluation. The readouts of all experiments, except lung pathology evaluation, could be assessed objectively. Mouse weight loss was determined using body weight measurement as a readout, and plaque assay or RT-qPCR was used to quantify viral burden. For lung study pathology, H&E stained tissue sections were scored by an experienced histopathologist blinded to the compositions of the groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Primary antibodies used: - In this study we used and analyzed antibodies C121, C135 and C144 against SARS-CoV-2 (in house production). - Anti-Zika virus monoclonal antibody Z021 (Robbiani et al, Cell 2017) used as isotype control - Anti-Histone H3 antibody, Cat. No.: ab1791 (Abcam), lot: GR3237685-2, dilution: 1:1000 - Anti-ACE2 antibody, Cat. No.: ab15348 (Abcam), lot: GR3333640-7, dilution: 1:1000 - F4/80 (D2S9R) XP® Rabbit mAb (Cat.#70076) Cell Signaling Technology, USA, Lot 5, RRID AB_2799771, dilution 1:800

Following secondary antibodies were used:
- Goat Anti-Mouse IgG, Human ads-AP, Cat.-No.: 1030-04 (SouthernBiotech, dilution 1:500)
- Goat Anti-Human IgG-AP, Cat.-No.: 2040-04 (SouthernBiotech, dilution 1:500)
- HRP-Polymer anti-Rabbit (Ready-to-use), Zytomed, Germany, Cat. # ZUC 032-100, Lot A0880-4 (no dilution)
- Goat Anti-Rabbit IgG H&L (HRP), Cat. No.: ab205718 (Abcam), lot: GR3269880-1, dilution: 1:10000

Validation

The human monoclonal antibody Z021, which binds to the Envelope Domain III of the Zika virus, was previously reported and validated (PMID: 31413072).
No validation statements for the other antibodies that are commercially available.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Expi293F cells (Thermo Fisher Scientific)
293 [HEK-293] cell line (CRL-1573™) (ATCC®)
293AAV cell line (AAV-100) (Cell Biolabs, Inc)
Neuro-2a cell line (CCL-131™) (ATCC®)
Vero E6 (CRL-1586™) (ATCC®)
293TAce2 (derived from 293T as reported in Robbiani et al. Nature, DOI: 10.1038/s41586-020-2456-9)

Authentication

Not authenticated after purchase

Mycoplasma contamination

In situ analysis never detected Mycoplasma infection.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell line have been used in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals

Mice C57Bl/6NCrl (females, 13-15 weeks old). Mice were housed in individually ventilated cages (Green line, Tecniplast, Italy) in the controlled environment with a 12/12 hour light-dark cycle, 20-22 °C and 45-65% humidity. Animals were fed the standard chow diet (1314 Altromin, Germany) ad libitum. Drinking water was filtered by reverse osmosis and chlorinated to 1.5 ppm. Water bottles were changed weekly.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not invovle field-collected samples.

Ethics oversight

The experiments were approved by the Committee on the Ethics of Animal Experiments of the Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, Institute of Molecular Genetics of the Czech Academy of Sciences, and of the Departmental Expert Committee for the Approval of Projects of Experiments on Animals of the Academy of Sciences of the Czech Republic (permits 82/2020 and 101/2020).

Note that full information on the approval of the study protocol must also be provided in the manuscript.